Office Action Summary	Application No.	Applicant(s)	
	09/870,358	OON ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6, 7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed July 30, 2002. Currently, claims 1-7, 10 are pending.

Election/Restrictions

2. Applicant's election without traverse of Group I (Claims 1-7, 10) in Paper No. 9 is acknowledged.

Priority

3. This application claims priority to foreign application Singapore 20004041-0, filed July 18, 2000. A certified copy of the application has been provided.

Specification

4. The specification contains a brief description of the drawings on page 5-6. The description of Figure 1 does not describe both part A and B separately as required. Appropriate correction is required.

Information Disclosure Statement

5. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

The bibliography on page 34 is not a proper information disclosure statement.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-7, 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-5 are indefinite over the recitation "capable of hybridizing" because capability is a latent characteristic and the claims do not set forth the criteria by which to determine capability. That is, it is not clear whether the recited primers have the potential to hybridize or do in fact hybridize the target strand. Amendment of the claim to read, for example, "which hybridize to the target strand" would obviate this rejection.

B) Claims 2-4 are indefinite over the recitation "corresponding to" in Claims 2 and 3 because it is unclear what corresponding to encompasses. It is unclear whether corresponding to requires that they are the conserved nucleotide sequence or whether they are not the conserved regions, but a region which is in the same location as a conserved nucleic acid or may differ from the conserved region in some way. The claim may be amended to recite "wherein the primers hybridize to the conserved nucleotide sequence or a region flanking a conserved nucleotide sequence". Moreover, "within a part" is indefinite because it is unclear whether the primer need only comprise a part of the sequence encoding HbsAg, namely an A, T, G or C or whether "a part" is intended

to mean the primer consists of a fragment of HbsAg. Thus it is unclear to what degree of similarity the "part" must have with the HbsAg sequence.

C) Claim 10 is indefinite over the recitation <400>1 and <400>2. It is unclear what this notation means. In the event that applicant intended to recite a primer selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 2, appropriate amendment is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 2, 3, 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Mbayed et al. (J. Clinical Microbiology, Vol. 36, No. 11, pages 3362-3365, November 1998).

Mbayed et al. teaches a method for detecting HBV nucleic acid target sequence in a sample, namely serum samples by amplifying the DNA using a nested PCR method to amplify part of the surface gene (page 3362, col. 2)(limitations of Claim 1). The extracted DNA was amplified with primers and then a second round of primer including primers HBS1 and HBS2. The HBS1 primer is 20 nucleotides in length. SEQ ID NO: 1 of the instant application comprises each of the 20 nucleotides of HBS1 with an

additional T nucleotide on the 3' end. HBS2 is immediately downstream of SEQ ID NO: 2 of the instant application. As seen in Figure 1, SEQ ID NO: 2 is positions 668-690 of the Figure. These nucleotide positions are conserved among the Gualeguay HBV isolates. The amplification product was sequenced as a means of detection. Therefore, Mbayed teaches a method for detecting an HBV derived nucleic acid target sequence in a sample.

8. Claims 1-3, 10 are rejected under 35 U.S.C. 102(b) as being anticipated by McDonough (US Pat. 5,780,219, July 14, 1998).

McDonough et al. (herein referred to as McDonough) teaches nucleic acid amplification oligonucleotides and probes to human hepatitis B virus. McDonough teaches a method of detecting HBV by denaturing a sample, namely 10 ml of plasma from samples was treated with 10 ml of 0.2N KOH at 95C for 15 minutes (col. 6, lines 20-40)(limitations of Claim 1a). McDonough teaches contacting the denatured sample with a set of primers comprising at least two primers which hybridize to the target and are extended, namely a buffer containing reagents for amplification was added and incubated (col. 6, lines 20-40)(limitations Claim 1b and 1c). The reaction was then analyzed for the presence for the amplified product (col. 6, lines 20-40)(limitations of Claim 1d). McDonough teaches using amplification oligonucleotides useful for specific detection of human hepatitis B virus in an amplification assay (col. 2, lines 40-68). The amplification oligonucleotides are complementary to a conserved region of HBV genomic nucleic acid and are nucleotide polymers able to hybridize to the nucleic acid

of HBV corresponding to HBV sequence adw bases 365-389, 455-479, 466-490, 1415-1436, 1557-1587, 2301-2333, 2418-2442, or 2421-2444. McDonough exemplifies SEQ ID NO: 4-12 as oligonucleotides which are specific for detection of HBV. SEQ ID NO: 5, position 25-5, of McDonough encompasses the complement of SEQ ID NO: 1 of the instant application. Moreover, SEQ ID NO: 2 of the instant application would hybridize under low stringency conditions to any number of the oligonucleotides provided by McDonough. Therefore, McDonough teaches every limitation of the claimed invention.

9. Claims 1, 2, 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Weinberger et al. (Viral Hepatitis and Liver Disease, pages 138-143, Torino, Edizioni Minerva Medica, 1997).

Weinberger et al. (herein referred to as Weinberger) teaches a method of amplification and detection of HBV DNA. Viral DNA was isolated from serum. Primer sequences, which represent highly conserved regions of the s-gene (Tab 1) were added to the template DNA. Both the first and second round amplification comprised an initial denaturation step. The amplification was detected and visualized on agarose gels (page 139, col. 1). Therefore, since Weinberger teaches every limitation of the claims, Weinberger anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mbayed et al. (J. Clinical Microbiology, Vol. 36, No. 11, pages 3362-3365, November 1998).

This rejection is applied in the event that applicant's amend their claims to require that the primers consist of SEQ ID NO: 1 and 2.

Mbayed et al. teaches a method for detecting HBV nucleic acid target sequence in a sample, namely serum samples by amplifying the DNA using a nested PCR method to amplify part of the surface gene (page 3362, col. 2)(limitations of Claim 1). The extracted DNA was amplified with primers and then a second round of primer including primers HBS1 and HBS2. The HBS1 primer is 20 nucleotides in length. SEQ ID NO: 1 of the instant application comprises each of the 20 nucleotides of HBS1 with an additional T nucleotide on the 3' end. HBS2 is immediately downstream of SEQ ID NO:

2 of the instant application. As seen in Figure 1, SEQ ID NO: 2 is positions 668-690 of the Figure. These nucleotide positions are conserved among the Gualeguay HBV isolates. The amplification product was sequenced as a means of detection. Mbayed teaches phylogenetic analysis shows "a clear different between the genotype distribution in Buenos Aires, a low-prevalence area, and that found in Gualeguay, Entre Rios, a high prevalence area" (abstract).

Mbayed does not specifically teach modifying the primers to obtain alternative primers, namely SEQ ID NO: 1 and 2.

However, since the claimed oligonucleotides simply represent functional equivalents of the primers taught in the art, the skilled artisan would have been motivated to have designed additional primers which amplified HBV nucleic acids. Given the teachings of Mbayed aligning HBV isolates, the ordinary artisan would have recognized alternative primers which are also within conserved regions of the HBV nucleic acids would be equivalents to the HBS1 and HBS2 primers. The skill in the art at the time the invention was made was very high with respect to designing species or isolate specific primers. Therefore, the ordinary artisan would have recognized that designing primers to regions which differ among isolates enable the distinction between the isolates. For example, designing primers to regions which are conserved among Gualeguay isolates but which diverge from Buenos Aires isolates enables the differentiation between the two subpopulations. The ordinary artisan would therefore have the alignment of Mbayed to facilitate designing of nucleic acid primers which would function to amplify HBV isolates from Gualeguay. Since Mbayed teaches that there is a

clear different between the distribution in low and high prevalence areas, the ordinary artisan would be motivated to have analyzed populations in order to determine whether the populations were at risk for HBV.

12. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mbayed et al. (J. Clinical Microbiology, Vol. 36, No. 11, pages 3362-3365, November 1998) or McDonough (US Pat. 5,780,219, July 14, 1998) or Weinberger et al. (Viral Hepatitis and Liver Disease, pages 138-143, Torino, Edizioni Minerva Medica, 1997) and further in view of Mason et al. (Hepatology, Vol. 27 (6) 1736-42, June 1998).

Mbayed et al. teaches a method for detecting HBV nucleic acid target sequence in a sample, namely serum samples by amplifying the DNA using a nested PCR method to amplify part of the surface gene (page 3362, col. 2)(limitations of Claim 1). The extracted DNA was amplified with primers and then a second round of primer including primers HBS1 and HBS2. The HBS1 primer is 20 nucleotides in length. SEQ ID NO: 1 of the instant application comprises each of the 20 nucleotides of HBS1 with an additional T nucleotide on the 3' end. HBS2 is immediately downstream of SEQ ID NO: 2 of the instant application. As seen in Figure 1, SEQ ID NO: 2 is positions 668-690 of the Figure. These nucleotide positions are conserved among the Gualeguay HBV isolates. The amplification product was sequenced as a means of detection. Therefore, Mbayed teaches a method for detecting an HBV derived nucleic acid target sequence in a sample.

McDonough et al. (herein referred to as McDonough) teaches nucleic acid amplification oligonucleotides and probes to human hepatitis B virus. McDonough teaches a method of detecting HBV by denaturing a sample, namely 10 ml of plasma from samples was treated with 10 ml of 0.2N KOH at 95C for 15 minutes (col. 6, lines 20-40)(limitations of Claim 1a). McDonough teaches contacting the denatured sample with a set of primers comprising at least two primers which hybridize to the target and are extended, namely a buffer containing reagents for amplification was added and incubated (col. 6, lines 20-40)(limitations Claim 1b and 1c). The reaction was then analyzed for the presence for the amplified product (col. 6, lines 20-40)(limitations of Claim 1d). McDonough teaches using amplification oligonucleotides useful for specific detection of human hepatitis B virus in an amplification assay (col. 2, lines 40-68). The amplification oligonucleotides are complementary to a conserved region of HBV genomic nucleic acid and are nucleotide polymers able to hybridize to the nucleic acid of HBV corresponding to HBV sequence adw bases 365-389, 455-479, 466-490, 1415-1436, 1557-1587, 2301-2333, 2418-2442, or 2421-2444. McDonough exemplifies SEQ ID NO: 4-12 as oligonucleotides which are specific for detection of HBV. SEQ ID NO: 5, position 25-5, of McDonough encompasses the complement of SEQ ID NO: 1 of the instant application. Moreover, SEQ ID NO: 2 of the instant application would hybridize under low stringency conditions to any number of the oligonucleotides provided by McDonough. Therefore, McDonough teaches every limitation of the claimed invention.

Weinberger et al. (herein referred to as Weinberger) teaches a method of amplification and detection of HBV DNA. Viral DNA was isolated from serum. Primer

sequences, which represent highly conserved regions of the s-gene (Tab 1) were added to the template DNA. Both the first and second round amplification comprised an initial denaturation step. The amplification was detected and visualized on agarose gels (page 139, col. 1). Therefore, since Weinberger teaches every limitation of the claims, Weinberger anticipates the claimed invention.

Neither Mbayed nor McDonough nor Weinberger specifically teach reverse transcribing mRNA into cDNA prior to analysis.

However, Mason et al. (herein referred to as Mason) teaches hepatic nucleic acid extracts were assessed by PCR for either reverse-transcribed HBV RNA.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the methods of either Mbayed or McDonough or Weinberger with the teachings of Mason for reverse transcribing the HBV RNA prior to analysis to obtain DNA. The ordinary artisan would have been motivated to have reverse transcribed the HBV RNA into cDNA for the expected benefit of obtaining DNA which is more stable than RNA. Mason teaches that the reverse transcribed cDNA may be further analyzed by PCR.

13. Claims 5, 6, 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mbayed et al. (J. Clinical Microbiology, Vol. 36, No. 11, pages 3362-3365, November 1998) or McDonough (US Pat. 5,780,219, July 14, 1998) or Weinberger et al. (Viral Hepatitis and Liver Disease, pages 138-143, Torino, Edizioni Minerva Medica, 1997) and further in view of Dattagupta (EP 0 374 665, June 27, 1990).

Mbayed et al. teaches a method for detecting HBV nucleic acid target sequence in a sample, namely serum samples by amplifying the DNA using a nested PCR method to amplify part of the surface gene (page 3362, col. 2)(limitations of Claim 1). The extracted DNA was amplified with primers and then a second round of primer including primers HBS1 and HBS2. The HBS1 primer is 20 nucleotides in length. SEQ ID NO: 1 of the instant application comprises each of the 20 nucleotides of HBS1 with an additional T nucleotide on the 3' end. HBS2 is immediately downstream of SEQ ID NO: 2 of the instant application. As seen in Figure 1, SEQ ID NO: 2 is positions 668-690 of the Figure. These nucleotide positions are conserved among the Gualeguay HBV isolates. The amplification product was sequenced as a means of detection. Therefore, Mbayed teaches a method for detecting an HBV derived nucleic acid target sequence in a sample.

McDonough et al. (herein referred to as McDonough) teaches nucleic acid amplification oligonucleotides and probes to human hepatitis B virus. McDonough teaches a method of detecting HBV by denaturing a sample, namely 10 ml of plasma from samples was treated with 10 ml of 0.2N KOH at 95C for 15 minutes (col. 6, lines 20-40)(limitations of Claim 1a). McDonough teaches contacting the denatured sample with a set of primers comprising at least two primers which hybridize to the target and are extended, namely a buffer containing reagents for amplification was added and incubated (col. 6, lines 20-40)(limitations Claim 1b and 1c). The reaction was then analyzed for the presence for the amplified product (col. 6, lines 20-40)(limitations of Claim 1d). McDonough teaches using amplification oligonucleotides useful for specific

detection of human hepatitis B virus in an amplification assay (col. 2, lines 40-68). The amplification oligonucleotides are complementary to a conserved region of HBV genomic nucleic acid and are nucleotide polymers able to hybridize to the nucleic acid of HBV corresponding to HBV sequence adw bases 365-389, 455-479, 466-490, 1415-1436, 1557-1587, 2301-2333, 2418-2442, or 2421-2444. McDonough exemplifies SEQ ID NO: 4-12 as oligonucleotides which are specific for detection of HBV. SEQ ID NO: 5, position 25-5, of McDonough encompasses the complement of SEQ ID NO: 1 of the instant application. Moreover, SEQ ID NO: 2 of the instant application would hybridize under low stringency conditions to any number of the oligonucleotides provided by McDonough. Therefore, McDonough teaches every limitation of the claimed invention.

Weinberger et al. (herein referred to as Weinberger) teaches a method of amplification and detection of HBV DNA. Viral DNA was isolated from serum. Primer sequences, which represent highly conserved regions of the s-gene (Tab 1) were added to the template DNA. Both the first and second round amplification comprised an initial denaturation step. The amplification was detected and visualized on agarose gels (page 139, col. 1). Therefore, since Weinberger teaches every limitation of the claims, Weinberger anticipates the claimed invention.

Neither Mbayed nor McDonough nor Weinberger specifically teach the use of a labeled primer or a primer attached to a solid support in combination with a primer in solution.

However, Dattagupta specifically teaches a method for amplifying and detecting specific target nucleic acid sequences in a sample by contacting a first primer and a

second primer with nucleic acid where one primer is immobilized and the other primer is labeled (Table 1, embodiments (3) and (6); page 4)(limitations of Claims 6-7). Dattagupta teaches that embodiments (3) and (6) of Table 1 may be assayed for using detection of the label on the support to determine the presence of the test amplified nucleic acid; by hybridization with a specific probe; extent of incorporation of a labeled nucleic acid residue; or a post extension agglutination reaction (page 4, lines 36-43). Dattagupta teaches that in an "immobilizable/labeled system, the biotin would be present on one primer and a lable such as fluorescein would be on the second primer, following amplficiation by thermocycling, the biotin containing product could be immobilized" (page 7, lines 12-16)(limitations of Claim 5). Dattagupta provides that the improvement of the method over the Mullis patent is at least one of the primers is immobilized (page 3, line 34-35). Additionally, Dattagupta teaches that the PCR method is significantly improved by the use of immobilized or immobilizable nucleic acid primers. The final amplified products are already immobilized or specifically immobilizable without significant loss in efficiency of amplification (page 5, lines 9-12).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the PCR methods of Mbayed nor McDonough nor Weinberger with the teachings of Dattagupta of the improvements of immobilization for detection of PCR products. The ordinary artisan would have been motivated to have immobilized and labeled the primers of Mbayed nor McDonough nor Weinberger for the express benefits taught by Dattagupta. Dattagupta teaches that the "PCR method is significantly improved by the use of immobilized or immobilizable nucleic acid primers. The final

amplified products are already immobilized or specifically immobilizable without significant loss in efficiency of amplification." Therefore, the ordinary artisan would have been motivated to have immobilized and labeled the primers in the HBV detection methods for the express benefit of improved detection.

Conclusion

14. No claims allowable over the art.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg
October 21, 2002

Jehanne Souaya
JEHANNE SOUAYA
PATENT EXAMINER
October 21, 2002